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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,248	04/02/2004	Sherin S. Abdel-Meguid	50201/003002	3934

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 08/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,248	ABDEL-MEGUID ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-103* is/are pending in the application.

4a) Of the above claim(s) *1-99,101 and 103* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100 and 102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 April 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group XX, claims 100 and 102 in the reply filed on June 20, 2005 is acknowledged.

Claims 1-99, 101, and 103 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 20, 2005.

Claims 100 and 102 have been examined on the merits.

Specification

The disclosure is objected to because of the following informalities:

As provided in 37 CFR 1.77(b), the specification of a utility application should include a section INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC:

> (e) Incorporation-By-Reference Of Material Submitted On a Compact Disc: The specification is required to include an incorporation-by-reference of electronic documents that are to become part of the permanent United States Patent and Trademark Office records in the file of a patent application. See 37 CFR 1.52(e) and MPEP § 608.05.

Applicant identifies the material submitted on CD in the Figure 16 description (page 72) and states that it is 'incorporated by reference' in Figure 16, but does not make an 'incorporation by reference' statement in the specification.

The use of the trademark(s), e.g., Insight II and SYBYL (page 33), has/have been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant should capitalize each letter of the word or include a proper trademark symbol, such as ™ or ® following the word. Further, language such as "the product X (a descriptive name) commonly known as Y (trademark)" is impermissible, since such language does not bring out the fact that the latter is a trademark. Language such as "the product X (a descriptive name) sold under the trademark Y" is permissible. See MPEP § 608.01 (v).

Appropriate correction is required.

Drawings

The drawings are objected to because although Applicant has complied with the sequence rules, sequences of the figures (Figures 2, 6, 7, and 9) must be accompanied by the identifying SEQ ID NO.

Further, 'incorporation by reference' is not proper in figure 16, and must be in the specification, as set forth *supra*.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 100 and 102 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

In the instant case, the claims are drawn to a myriad of mutant Factor XI proteins or fragments, wherein the mutation a) enhances crystallization of the catalytic domain, b) is "a

mutation of a residue that is otherwise post-translationally modified in an organism used for recombinant expression", c) alters the charge, d) eliminates a free, reactive sulfhydryl of a cysteine, e) alters the charge density without altering the overall charge, f) is an N- or C-terminal residue mutation, or g) alters the folding.

(1) Level of skill and knowledge in the art:

The level of skill and knowledge in the art is high, with regards to protein synthesis.

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

RUDINGER (J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (Page 6).

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable.

BERENDSEN (H.J.C. Berendsen. A Glimpse of the Holy Grail? Science (1998) 282, pages 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics." (Page 642). Berendsen states that, "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free

energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field. (Page 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). VOET (D. Voet and J.G. Voet. Biochemistry, 2nd Edition.(1995), pages 235-241) teaches that the mutant hemoglobin HbE [Glu B8(26)β → Lys] has, "no clinical manifestations in either heterozygotes or homozygotes." (Page 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which result in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state. Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state). (Page 236).

HbS is a single point mutation, Val → Glu A3(6)β (Page 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

SMILEK (D.E. Smilek, *et al.* Proc. Natl. Acad. Sci. USA (1991) 88, pages 9633-9637) teaches that a single amino acid substitution in the myelin basic protein peptide, "confers the capacity to prevent rather than induce EAE even after peptide-specific encephalitogenic T-cells have been activated." (Abstract).

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is highly unpredictable, and can produce an effect opposite

to that which is desired, it flows logically that one could not predict *a priori* the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties.

(2) Partial structure:

The claims provide that the product is a mutant of Factor XI (FXI). The specification provides for 'alanine screening' mutants at S434 (S434A) and T475 (T475A), each alone or in combination with the other. Additionally, the specification provides for the S434/T475 mutation in combination with the following mutations: K422A, K437A, K486A, K505A, and K509A, as well as AVC-terminal truncation; and S434A/T475A with C482S, alone or in combination with K437A, R479A, K505A, D476A, and Y416S.

The specific structure of FXI is not described in the claims, e.g.- human, mouse, or rat, by a specific sequence. The specification provides three sequences of FXI from three different sources: Homo sapiens (Human), Oryctolagus cuniculus (European Rabbit), and Mus musculus (mouse).

The sequences do not show the residues, e.g S434, T475, etc. which are claimed to be mutated, and does not describe sufficiently an example of FXI which has the starting amino acid(s) which is/are mutated.

The specification and claims lack sufficient number and variety in the type of mutation(s) and sequences of FXI to sufficiently describe the genus.

(3) Physical and/or chemical properties:

The compound is FXI or a fragment with mutations. Some mutants must have altered/changed charge or have an altered folding pattern.

(4) Functional characteristics:

The claims and specification provide that the mutation a) enhances crystallization of the catalytic domain, b) is "a mutation of a residue that is otherwise post-translationally modified in an organism used for recombinant expression", c) alters the charge, d) eliminates a free, reactive sulfhydryl of a cysteine, e) alters the charge density without altering the overall charge, f) is an N- or C- terminal residue mutation, or g) alters the folding.

The specification lacks sufficient description of all mutations which would have the asserted function, and does not provide sufficient variance in the genus to fully describe the myriad of mutations which are embraced by the generic. Further, the specification does not correlate mutation(s) of FXI with the asserted functions beyond those disclosed *supra*.

(5) Method of making the claimed invention:

Methods of making proteins and peptide fragments are well known in the art, e.g. Merrifield peptide synthesis and recombinant methods.

The specification does not provide sufficient description on how one would make mutants with the asserted functions, e.g. a mutation that alters the folding of FXI, providing only specific point mutations. Further the specification only provides description for a limited number of amino acid substitutions, but does not describe the myriad of 'mutations' embraced by the generic term, such as chemical modification of the amino acid(s).

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims 100 and 102 are broad generic claims, with respect to all possible FXI mutant proteins and fragments encompassed by the claims. The possible structural variations are limitless to any class of FXI

mutant protein or fragment. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, e.g. 'a mutation that alters folding' or 'alters the charge density', the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. While having written description of the specific mutations claimed in claim 102 for FXI which has the specific starting amino acids, e.g. S434, T475, the specification is void of sufficient variety of specific mutations or a correlation between the mutation(s) and the desired function.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 100 and 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons set forth herein:

Claim 100 recites, 'protein or fragment' in the preamble, however the mutations are drawn to FXI, not to FXI or fragments of FXI, and thus it is unclear how a mutation of a fragment of FXI would alter, e.g. folding of a FXI protein, and thus the claims are indefinite.

Claim 100 recites, 'enhances the ability' to crystallize, which is a relative term and is indefinite because 'enhancement' is subjective and requires a benchmark from which a comparison can be made, e.g. 'relative to the wild-type'.

Claim 102 is drawn to FXI mutants with specific point mutations. It is unclear as to which FXI applicant is claiming as the starting point for making the mutants, and thus it is unclear as to how one could make the desired mutants, as the three species (SEQ ID NOs: 1-3) disclosed in the specification lack the requisite starting amino acids, e.g. S434 or an AVC C-terminus from which one could derive the claimed mutants.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 100 is rejected under 35 U.S.C. 102(b) as being anticipated by SUN (M.-F. Sun, et al. J. Biol. Chem. (1999), 274(51), pages 36373-36378).

The instant claim is drawn to mutants of FXI.

Sun teaches 26 different FXI mutants (Table 1, page 36377; Figure 1, page 36374). Sun teaches that blocks of residues on FXI were substituted by alanine (e.g. mutant 22: FXI [T249A, R250A, I251A]; *see* Figure 1 caption for description).

Mutations of any kind will inherently 'alter the folding' of a protein, as side chain interactions will be altered. Further, R250A alters the charge of FXI and mutates a residue 'that

is otherwise post-translationally modified' – that is, a glycosylation site is removed by substitution with alanine.

Sun further teaches mutant 1: FXI [I183A, R184A, D185A] which alters the charge distribution, but not the overall charge, as R and D are oppositely charged amino acids – a net zero charge, which when substituted with A, become neutrally charged – changing the distribution of the charge, but not the overall FXI charge.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 100 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sun, as applied to claim 100, *supra*, in view of VERONESE (US Patent 5,286,637), DALBORG (US Patent 6,048,720), GAERTNER (H.F. Gaertner and R.E. Offord. Bioconj. Chem. (1996) 7(1), pages 38-44), and INADA (Y. Inada, et al. Methods Enzymol. (1994) 242, pages 65-90).

The instant claims are presented *supra*, wherein one mutation is N- or C-terminus residue mutation. The teachings of Sun are presented *supra*.

Sun does not teach terminal modification of FXI. PEGylation is considered to be a mutation of the residue, as the residue is no longer un-modified.

Gaertner teaches that, "Covalent attachment of monomethoxypoly(ethylene glycol) [mPEG] to therapeutic proteins prolongs their circulatory life time *in vivo*, reduces their antigenicity and immunogenicity, and improves their resistance to proteolysis. These properties are of great clinical interest, especially in the case of relatively small proteins, where it is believed that an increase of the Stoke's radius is consistent with a reduced renal clearance." (citations removed, page 38).

Veronese teaches that, "Modification of biologically active substances such as peptide or proteins with [mPEG] is reported to change extensively their physical, chemical, enzymological, immunological, as well as their pharmacological and pharmacokinetic properties." (column 1, lines 15-19).

Veronese teaches that, "Such modified peptide or protein derivatives exhibit some advantages when compared to the peptide or protein itself: increased water solubility, decreased antigenicity or increased half-life of the circulating peptide or protein." (column 1, lines 24-28).

Veronese teaches that, "It may have been found that some, if not all of the above mentioned drawbacks [difficulty incorporating radioactive probe, inactivation of enzyme, difficulty modulating cleavage, and difficulty introducing targeting sequences into the polymer-conjugate] can be eliminated or at least significantly reduced by making use of the new drug polymer derivatives of the invention which are represented by the generic formula RO-

$(CH_2CH_2O)_n$-(CO)-NH-X-(CO)-NH-Z" where R is a lower alkyl, n is between 25 and 500, NH-X-(CO) is an amino acid, or a di- or tri-peptide, NH-Z is either a biologically active peptide or NH_2, and (CO)-N represents a peptide bond (column 1, lines 41-58).

Dalborg teaches that, "It is well known, that the in-vitro stability and in-vivo half-life of polypeptides can be increase by covalently attachment of biocompatible polymers (in the following referred to as conjugation or modification). Modification of the polypeptide surface also has the advantage of decreasing immunogenicity exhibited by the polypeptide." (column 1, line 23+).

Dalborg further teaches that, "Pegylation, i.e. coupling of various [PEG] to a polypeptide, is a technique widely used for increasing the in-vitro stability and in-vivo half-life of e.g. proteins. In pegylation, many techniques have been proposed of the years." (column 1, line 30+).

Inada teaches that, "enzymes modified with a [PEG] derivative become more soluble and remain active in organic solvents. Because PEG is an amphipathic macromolecule, its hydrophilic nature makes it possible to modify enzymes in aqueous solution, and its hydrophobic nature would make modified enzymes soluble in hydrophobic environments. In fact, modified enzymes such as catalase and peroxidase have markedly high activities in organic solvents." (page 71).

Inada teaches, "The effect of the modification with [PEG] on the reduction of immunoreactivity depends on the molecular weight of the [PEG], the degree of modification of amino groups, and the shape of the modifiers (chain form or comb form). If the average molecular weight of [PEG] is lower than 5000, serious reduction in the enzymatic activity results

without complete elimination of immunoreactivity. Therefore, [PEG] with a molecular weight of more than 5000 is recommended as a modifier." (page 87, discussed with regards to Asparaginase activity).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have PEGylated the FXI, generating a 'mutation of the N- or C-terminus residue', because PEGylation increases the biological half-life and retain the biological activity of the peptides to which they are attached ("inhibiting proteolytic activity is better sustained throughout time"), as taught by Dalborg, and Gaertner.

One would have been motivated to make the PEGylated FXI for the benefit of increasing solubility in both aqueous and organic solvents, increasing the half-life and clearance time, reducing both antigenicity and immunogenicity, and improving the resistance to proteolysis, while retaining biological activity of the FXI.

One of ordinary skill in the art would have had a reasonable expectation for success in making the PEGylated FXI, as PEGylation of peptides is a routine technique widely practiced in the peptide arts for the reasons stated *supra*, as taught by Dalborg, Gaertner, Inada, and Veronese.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

NO CLAIMS ARE ALLOWED.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571)272-0974. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

8/4/06
ANISH GUPTA
PRIMARY EXAMINER

Andrew D. Kosar, Ph.D.
Art Unit 1654